# Does setting the breathing machine (ventilator) to deliver breaths using a method called airway pressure release ventilation help patients with diseased lungs to heal faster and spend less time on a ventilator?

Submission date	<b>Recruitment status</b> Recruiting	[X] Prospectively registered		
12/06/2024		[X] Protocol		
Registration date	Overall study status	Statistical analysis plan		
21/06/2024	Ongoing  Condition category	Results		
Last Edited		Individual participant data		
12/09/2025	Respiratory	[X] Record updated in last year		

# Plain English summary of protocol

Background and study aims

Around half of all patients in critical care need help from a breathing machine (ventilator) to maintain oxygen levels. Although they may be life-saving, breathing machines can cause damage to diseased lungs and make chest infections more likely.

The usual way a breathing machine is used aims to protect the lungs from damage until they are healed. However, damage can still occur, and the lungs take time to recover. Airway pressure release ventilation (APRV) is a way of using the breathing machine that we think causes less damage. It moves gas into the lungs gently over a longer time. This helps to reduce lung damage, helping faster healing. APRV may reduce time on the breathing machine and in the hospital which may save costs. APRV may also reduce the risk of death.

The aim of this study is to find out if setting the breathing machine to deliver breaths using APRV helps patients with diseased lungs to heal faster and spend less time on a ventilator compared to the usual way breathing support is given in critical care. The researchers also want to know if APRV saves more lives, improves quality of life, and saves the NHS money by helping people leave CCU sooner.

# Who can participate?

Patients admitted to a CCU in the UK who are:

- 1. Aged 18 years or more
- 2. Receiving support from a breathing machine
- 3. Have moderate to severely low oxygen levels
- 4. Are expected by the critical care team to stay on a breathing machine for more than 2 days

# What does the study involve?

Participants will be assigned by chance (randomised) to one of two groups.

1. APRV: The breathing machine will be set to the APRV mode. APRV moves gas into the lungs

gently over a longer time. APRV is available on all ventilators that are used within the NHS.

2. Usual care: The breathing machine will be set as usual by the critical care team.

There will be no other changes to care delivered by the critical care team for patients in both the APRV and usual care group.

Participants, the research team, or the critical care team will not be able to choose which group your relative/friend is in. This is decided by a computer at random, just like tossing a coin or drawing lots.

The research team will collect information about the care the participants receive while in critical care including how the breathing machine is used, how long they need the machine, and how long they stay in critical care. The research team will collect the participants' personal information such as age, ethnicity, sex and past medical conditions before coming to critical care as this helps them to understand the effect of APRV on different groups of people.

After leaving the hospital, participants will be sent a questionnaire 2 and 6 months after hospital discharge asking about their overall wellbeing and quality of life. Each questionnaire will take about 5 to 10 minutes to complete. If needed, someone can complete them on the participant's behalf. The researchers will share the participant's name, email address, and phone number with a third-party company in order to send them the questionnaires by text message or email. They may also get in touch with participants by text message or email if we have any queries about their questionnaire or if we have any updates related to the study.

What are the possible benefits and risks of participating?

As this is a study, participants may or may not benefit from taking part. However, the findings of the research will help to improve the treatments and care provided to patients with a similar condition now and in the future.

There is no payment for taking part in this study. However, to thank participants for their time in completing the follow-up questionnaires at 2 and 6 months, they will be given a small monetary gift voucher alongside each questionnaire.

The University of Warwick is currently leading several studies looking at how we treat patients with respiratory failure. This group of studies is called the 'Confederation of Respiratory Critical Care Trials' or 'CoReCCT'. If participants are taking part in other studies within CoReCCT, they will not need to complete questionnaires for each study. Participants will only be asked to complete the questionnaires once and will receive one voucher with each questionnaire. At this time, there are no important disadvantages or risks to taking part.

Where is the study run from?

Warwick University in partnership with NHS hospitals across the UK

When is the study starting and how long is it expected to run for? January 2024 to August 2027

Who is funding the study?

National Institute for Health Research, Health Technology Assessment (NIHR154501) (UK)

Who is the main contact? RELEASE trial manager, RELEASE@warwick.ac.uk

# Study website

https://warwick.ac.uk/fac/sci/med/research/ctu/trials/release/

# Contact information

# Type(s)

Scientific, Principal Investigator

# Contact name

Prof Luigi Camporota

# **ORCID ID**

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# Contact details

Department of Critical Care Guy's & St Thomas' NHS Foundation Trust Westminster Bridge London United Kingdom SE1 7EH

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# Type(s)

Scientific, Principal Investigator

#### Contact name

Prof Danny McAuley

# **ORCID ID**

https://orcid.org/0000-0002-3283-1947

# Contact details

Wellcome-Wolfson Institute for Experimental Medicine The Queen's University of Belfast Belfast United Kingdom BT9 7BL

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# Type(s)

Public, Scientific

#### Contact name

Mr Jonathan Guck

# Contact details

Warwick Clinical Trials Unit Warwick Medical School University of Warwick Gibbet Hill Road Coventry United Kingdom CV4 7AL

# Additional identifiers

# **EudraCT/CTIS** number

Nil known

#### IRAS number

335630

# ClinicalTrials.gov number

Nil known

# Secondary identifying numbers

IRAS 335630, NIHR154501, CPMS 62929

# Study information

# Scientific Title

Airway Pressure Release Ventilation (APRV) vs conventional ventilation for patients with moderate to severe acute hypoxemic respiratory failure: the RELEASE trial

# Acronym

**RELEASE** 

# Study objectives

What is the clinical and cost-effectiveness of airway pressure release ventilation (APRV) for adults requiring invasive mechanical ventilation (IMV) for moderate-severe acute hypoxaemic respiratory failure (AHRF)?

# Ethics approval required

Ethics approval required

# Ethics approval(s)

- 1. Approved 08/07/2024, Wales REC 2 (The Cardiff North Inn by Accor, Circle Way East, Llanaderyn, Cardiff, CF23 9XF, United Kingdom; +44 (0)2922941119; Wales.REC2@wales.nhs.uk), ref: 24/WA/0128
- 2. Submitted 18/06/2025, Scotland A REC (NHS Lothian, Edinburgh, EH1 3EG, United Kingdom; +44 131 465 5680; Manx.Neill@nhslothian.scot.nhs.uk), ref: 25-SS-0056-IRAS-351070

# Study design

Multi-centre randomized allocation-concealed controlled open-label pragmatic parallel-group clinical and cost-effectiveness trial with an internal pilot

# Primary study design

Interventional

# Secondary study design

# Randomised parallel trial

# Study setting(s)

Hospital

# Study type(s)

Treatment

# Participant information sheet

See study outputs table

# Health condition(s) or problem(s) studied

Moderate to severe acute hypoxaemic respiratory failure (AHRF)

#### **Interventions**

Participants are randomised to either:

- 1. Early airway pressure release ventilation (APRV)
- 2. Standard conventional lung protective invasive mechanical ventilation (no APRV)

Participants will be randomised via randomly permuted blocks using an automated web-based system on a one-to-one basis, stratified by site and prior enrolment into the Awake Prone Positioning and Protect Airways trials, using a computer-generated randomisation schedule managed by the Warwick CTU. The researchers have selected a parallel group RCT design to minimise selection bias and ensure against accidental bias.

The intervention (APRV or control) will continue until one of the following criteria is met:

- 1. 60 days after randomisation
- 2. Successful unassisted breathing (at 48 hours with no further requirement for inspiratory support or extracorporeal lung support. See section 2.4.3 for the full definition)
- 3. Trial intervention-related serious adverse event
- 4. Death or discontinuation of active treatment
- 5. Withdrawal of consent

# Intervention Type

Other

# Primary outcome measure

Current primary outcome measure as of 25/06/2025:

Duration of mechanical ventilation (defined as the time from randomisation to first successful unassisted breathing or death) measured using data collected from site staff at the time of first successful unassisted breathing or death

Previous primary outcome measure:

Duration of invasive mechanical ventilation (defined as the time from randomisation to first successful unassisted breathing or death) measured using data collected from site staff at the time of first successful unassisted breathing or death

# Secondary outcome measures

Current secondary outcome measures as of 25/06/2025:

- 1. All-cause mortality measured using data collected from site staff at 2 and 6 months
- 2. Time to first successful extubation
- 3. Need for reintubation prior to achieving first successful unassisted breathing
- 4. Use of non-invasive ventilation following extubation but prior to achieving first successful unassisted breathing
- 5. CCU and hospital length of stay measured using data collected from site staff at time of CCU and hospital discharge
- 6. Serious adverse events measured using data collected from site staff up to time of hospital discharge
- 7. Health-related quality of life measured using the 5-level EQ-5D version (EQ-5D-5L) at 2 and 6 months
- 8. Acute health care use measured using participant-completed resource use questionnaires and, if available, enriched using data obtained from site staff or linkage at 2 and 6 months
- 9. Within-trial cost-utility analysis from an NHS hospital care perspective using data collected from site staff and data obtained through linkage to routine datasets at 2 and 6 months

# Previous secondary outcome measures:

- 1. All-cause mortality measured using data collected from site staff at 2 and 6 months
- 2. Time to first extubation measured using data collected from site staff at time of extubation
- 3. Reintubation measured using data collected from site staff at time of reintubation
- 4. Use of non-invasive ventilation following extubation measured using data collected from site staff at time of extubation
- 5. CCU and hospital length of stay measured using data collected from site staff at time of CCU and hospital discharge
- 6. Serious adverse events measured using data collected from site staff up to time of hospital discharge
- 7. Health-related quality of life measured using the 5-level EQ-5D version (EQ-5D-5L) at 2 and 6 months
- 8. Acute health care use measured using participant-completed resource use questionnaires and, if available, enriched using data obtained from site staff or linkage at 2 and 6 months
- 9. Within-trial cost-utility analysis from an NHS hospital care perspective using data collected from site staff and data obtained through linkage to routine datasets at 2 and 6 months

# Overall study start date

01/01/2024

# Completion date

31/08/2027

# **Eligibility**

# Key inclusion criteria

Current inclusion criteria as of 25/06/2025:

- 1. Age ≥18 years
- 2. Receiving invasive mechanical ventilation
- 3. Moderate to severe acute hypoxaemic respiratory failure, defined as a single measurement showing a PaO₂/FiO₂ ratio <20 kPa while receiving a Positive End-Expiratory Pressure (PEEP) of ≥5 cmH₂O, assessed at any point within the first 60 hours after the initiation of invasive mechanical ventilation
- 4. Expected to stay on invasive mechanical ventilation for >48 hours

#### Previous inclusion criteria:

- 1. Age ≥18 years
- 2. Receiving invasive mechanical ventilation
- 3. Moderate to severe AHRF (PaO2/FiO2 <20 kPa with Positive End Expiratory Pressure (PEEP) ≥5 cmH2O) assessed at the time of screening (or as documented in the medical record in the preceding 2 hours)
- 4. Expected to stay on invasive mechanical ventilation for >48 hours

# Participant type(s)

Patient

# Age group

Adult

# Lower age limit

18 Years

### Sex

Both

# Target number of participants

710

# Key exclusion criteria

Current exclusion criteria as of 25/06/2025:

- 1. Receiving IMV ≥60 hours at the time of screening as will be unable to deliver early APRV
- 2. Primary reason for invasive mechanical ventilation is one of the following:
- 2.1. Asthma
- 2.2. Severe COPD
- 2.3. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)
- 2.4. Existing neuromuscular disease such as motor neurone disease, Guillain Barre or myasthenia gravis (as the cause of respiratory failure is not primarily lung-related)
- 3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)\*
- 4. Severe hypercapnic respiratory acidosis (pH <7.20 on the arterial blood gas assessed for trial inclusion)\*
- 5. Ongoing air leak (e.g. unresolved pneumothorax at time of screening)\*
- 6. Traumatic brain injury with uncontrolled intracranial hypertension\*

- 7. Likely death or treatment withdrawal in the next 24 hours
- 8. Home ventilation or home oxygen therapy prior to admission
- 9. Receiving, or decision to commence, ECMO in the next 24 hours
- \*(patients can be recruited if this resolves and remain eligible)

### Previous exclusion criteria:

- 1. Receiving IMV ≥60 hours at the time of screening as will be unable to deliver early APRV
- 2. Primary reason for invasive mechanical ventilation is one of the following:
- 2.1. Asthma
- 2.2. Severe COPD
- 2.3. Pulmonary embolism (massive or sub-massive) (as cause of hypoxaemia is not primarily due to collapse of lung tissue)
- 2.4. Existing neuromuscular disease such as motor neurone disease, Guillain Barre or myasthenia gravis (as the cause of respiratory failure is not primarily lung-related)
- 3. Refractory shock (systolic blood pressure < 90 mmHg, despite fluid administration and vasoactive drugs)\*
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- 6. Traumatic brain injury with uncontrolled intracranial hypertension\*
- 7. Likely death or treatment withdrawal in the next 24 hours
- 8. Home ventilation or home oxygen therapy prior to admission
- \*(patients can be recruited if this resolves and remain eligible)

# Date of first enrolment

14/02/2025

Date of final enrolment

31/05/2027

# **Locations**

# Countries of recruitment

England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Guy's and St Thomas' NHS Foundation Trust

St Thomas' Hospital

Westminster Bridge Road London United Kingdom SE1 7EH

# Study participating centre Arrow Park Hospital

Arrowe Park Hospital Arrowe Park Road Wirral United Kingdom CH49 5PE

# Study participating centre Bedford Hospital

Icash Bedford Hospital Kempston Road Bedford United Kingdom MK42 9DJ

# Study participating centre University Hospital Bristol

Bristol Royal Infirmary Marlborough Street Bristol United Kingdom BS2 8HW

# Study participating centre Conquest Hospital

The Ridge St. Leonards-on-sea United Kingdom TN37 7RD

# Study participating centre Queen Alexandras Hospital

Southwick Hill Road Cosham Portsmouth United Kingdom PO6 3LY

# Study participating centre Tameside General Hospital

Fountain Street Ashton-under-lyne United Kingdom OL6 9RW

# Study participating centre Blackpool Teaching Hospitals NHS Foundation Trust

Victoria Hospital Whinney Heys Road Blackpool United Kingdom FY3 8NR

# Study participating centre Ipswich Hospital Utc

Ipswich Hospital Heath Road Ipswich United Kingdom IP4 5PD

# Study participating centre James Cook University Hospital

Marton Road Middlesbrough United Kingdom TS4 3BW

# Study participating centre Kingston Hospital

Galsworthy Road Kingston upon Thames United Kingdom KT2 7QB

# Study participating centre Medway NHS Foundation Trust

Medway Maritime Hospital Windmill Road Gillingham United Kingdom ME7 5NY

# Study participating centre Russells Hall Hospital

Pensnett Road Dudley United Kingdom DY1 2HQ

# Study participating centre Queen Elizabeth Hospital Lewisham

Stadium Road London United Kingdom SE18 4QH

# Study participating centre St Georges Hospital

Blackshaw Road Tooting London United Kingdom SW17 0QT

# Study participating centre Aintree University Hospital

Lower Lane Liverpool United Kingdom L9 7AL

# Study participating centre University Hospital Lewisham

Lewisham High Street

London United Kingdom SE13 6LH

# Study participating centre University Hospital of North Tees

Hardwick Road Hardwick Stockton-on Tees United Kingdom TS19 8PE

# Study participating centre William Harvey Hospital

Kennington Road Willesborough Ashford United Kingdom TN24 0LZ

# Study participating centre Milton Keynes University Hospital

Standing Way Eaglestone Milton Keynes United Kingdom MK6 5LD

# Study participating centre University Hospitals Plymouth NHS Trust

Derriford Hospital Derriford Road Derriford Plymouth United Kingdom PL6 8DH

# Study participating centre Countess of Chester Hospital Countess of Chester Health Park Liverpool Road

Chester United Kingdom CH2 1UL

# Study participating centre Darent Valley Hospital Darenth Wood Road Dartford United Kingdom

Study participating centre Kettering General Hospital Rothwell Road

Kettering United Kingdom NN16 8UZ

DA2 8DA

# Study participating centre Midland Metropolitan University Hospital

Grove Lane Smethwick United Kingdom B66 2QT

# Study participating centre The Royal Glamorgan Hospital

Ynysmaerdy Pontyclun United Kingdom CF72 8XR

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London

United Kingdom NW1 2PG

# Study participating centre Whittington Health NHS Trust

The Whittington Hospital Magdala Avenue London United Kingdom N19 5NF

# Sponsor information

# Organisation

University of Warwick

# Sponsor details

Research and Impact Services University House Gibbet Hill Road Coventry England United Kingdom CV4 8UW +44 (0)2476 575 733 sponsorship@warwick.ac.uk

# Sponsor type

University/education

# Website

https://warwick.ac.uk/fac/sci/med/research/ctu/

# **ROR**

https://ror.org/01a77tt86

# Funder(s)

# Funder type

Government

## **Funder Name**

Health Technology Assessment Programme

# Alternative Name(s)

NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

# **Funding Body Type**

Government organisation

# **Funding Body Subtype**

National government

#### Location

**United Kingdom** 

# **Results and Publications**

# Publication and dissemination plan

Planned publication in a peer-reviewed journal. The researchers will use a multi-modal dissemination strategy: open access publication in high-impact factor journals; presentation at relevant national/international scientific conferences; and communication with participant and family networks including social media and lay press with a lay results summary to participants.

# Intention to publish date

31/08/2028

# Individual participant data (IPD) sharing plan

The data-sharing plans for the current study are unknown and will be made available at a later date.

# IPD sharing plan summary

Data sharing statement to be made available at a later date

# **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version 2.0	13/06/2024	16/07/2024	No	No
Participant information sheet			25/06/2025	No	Yes
Protocol file	version 3.0	26/03/2025	25/06/2025	No	No